The Evaluation of Thiol/Disulfide Homeostasis and Oxidative DNA Damage in Patients with Obsessive Compulsive Disorder

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Objective: In this study, we aimed to examine thiol/disulfide homeostasis and oxidative DNA damage in patients with OCD and compare them with healthy controls.
Methods: Thirty-five patients previously diagnosed with OCD in Van Yuzuncu Yil University Department of Psychiatry and thirty-three healthy volunteers were included in the study. The severity of the symptoms was measured using the Yale-Brown Obsessive-Compulsive Scale. Five ml of blood samples were taken from the patient and control groups. The samples were stored at appropriate conditions until use. Leukocyte DNA was isolated and the levels of 8-hydroxy-2-deoxyguanosine (8-OHdG) and deoxyguanosine were detected to assess the oxidative DNA damage. The level of oxidative DNA damage was expressed as $8\text{-OHdG}/10^6\text{dG}$. Total thiol/native thiol levels were measured for thiol/disulfide homeostasis. The level of disulfide was determined by subtracting the native thiol value from the total thiol value and the result was divided by two. Results were given as percentages.
Results: The total and native thiol levels in patients with OCD were significantly lower, and the disulfide levels were significantly higher in patients with OCD than healthy control subjects. In addition, 8-OHdG, an indicator of DNA damage, was significantly lower in the control group compared to the patient group.
Conclusion: Increased levels of disulfide/native thiol and disulfide/total thiol in patients with OCD show that levels of oxidative stress were elevated and therefore, higher 8-OHdG levels in patients with OCD is a marker of oxidative DNA damage.

KEY WORDS: Obsessive-compulsive disorder; Thiol disulfide; DNA damage.

INTRODUCTION

While obsessions are involuntary, persistent, repetitive thoughts; impulses and images, compulsions are repetitive behaviors and mental actions which the person feels like he or she must comply and execute as the person feels obliged to perform in response to these obsessions [1]. It has been stated that genetic and environmental factors may affect the etiopathology of obsessive compulsive disorders (OCD), and patients with OCD suffer from functional damage in the orbital and frontal cortex of the brain, basal ganglion and thalamus, and due to this damage, functionality of some neurotransmitters have been impaired [2-5]. In addition, it has been reported that the etiology of OCD is affected by oxidative damage, and that the oxidative balance is impaired in other psychiatric diseases [6]. While the body produces free radicals, it also eliminates them by using various methods, which is a stable and balanced process [7]. Excessive free oxygen radicals can result in damage in cell membrane, degradation of DNA, protein carboxylation, lipid peroxidation, and cell death [8,9]. Tissues of central nervous system are highly prone to oxidative damage, and the metabolism has developed antioxidative mechanisms against oxidation [10]. The most significant enzymes for antioxidant mechanisms are superoxide dismutase, glutathione peroxidase, catalase and thiols [11].

Thiols can undergo oxidation and develop disulfide bonds. Free oxygen radicals attack the thiol groups of sulfur-containing amino acids, which result in oxidation,

and this is the first observable change in protein oxidation [12]. The thiol group of the cysteine amino acid is highly prone to oxidative attack, and the thiol radical formed by thiol groups by different mechanisms lead to the formation of disulfide bonds in proteins [12]. Thiol/disulfide balance plays vital roles in detoxification, intracellular signal transmission, defense against oxidizing agents, regulation of enzyme activity, and programmed cell death [13,14].

Recently, a number of studies have stated that thiol/disulfide homeostasis has been impaired in schizophrenia, autistic spectrum disorders, as well as neurological diseases such as migraine, epilepsy, and internal diseases such as diabetic nephropathy, and thus may play a role in the pathogenesis of many disorders [15-17].

In order to make a true assessment of thiol / disulfide homeostasis, it is necessary to measure both thiol and total thiol levels. Thiol/disulfide homeostasis cannot be assessed by measuring thiol alone [18,19]. Free oxygen radicals formed in the body over time damage both intracellular and extracellular structures and disrupt genetic codes by making permanent changes in DNA [20]. 8-hydroxy-2-deoxyguanosine (8-OHdG) is a marker that is thought to cause degradation in mitochondria after oxidation [21]. Normally, the damaged DNA is repaired by a number of cellular mechanisms after oxidation reactions and 8-OHdG, a mitochondrial marker of oxidative damage, is removed from the body. Ultimately, endogenous 8-OHdG can be detected in both blood and urine and is evaluated as an indicator of DNA damage. Therefore, endogenous 8-OHdG has been stated as a biomarker of DNA damage in some diseases [22].

Some studies have suggested that the levels of markers of oxidative stress are increased and the oxidative balance is disturbed in patients with OCD [23,24]. Basal ganglia containing high levels of catecholamine may play a role in the etiopathogenesis of OCD. Moreover, it has been reported that free oxygen radicals highly affect basal ganglia [24]. Since catecholamine metabolism is the main source of free oxygen radicals in the brain, it has been reported that increased levels of catecholamine in the brain are associated with damage caused by free oxygen radicals [6].

A number of publications evaluating oxidative stress in patients with OCD exist in the literature [25]. However, to the best of our knowledge, this is the first study evaluating thiol/disulfide homeostasis and oxidative DNA damage in OCD patients. Further studies can be conducted to examine the levels of oxidative balance and markers of DNA damage in patients with OCD who receive a regular or irregular treatment and those who do not receive a treatment, or to examine the relationship between these markers and disease duration. In this context, our study will provide important information on the oxidant-antioxidant status and levels of oxidative DNA damage in patients with OCD.

METHODS

This study was conducted at Van Yuzuncu Yil University Medical Faculty, Department of Psychiatry between January and September 2020. The institutional ethics committee approved the study with reference number 07/18.12.2019. All participants were informed about the study and a written consent was obtained from all participants.

Thirty-five patients diagnosed with OCD by a psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition diagnostic criteria at Van Yuzuncu Yil University Psychiatry Clinic were included in the study. Thirty-three volunteers consisted the control group.

The exclusion criteria were presence of metabolic, endocrine and neurological disorders, diabetes mellitus, pregnancy, obesity, smoking, alcohol and substance use disorders, other psychiatric pathologies, mental retardations, psychosis, schizophrenia, mood disorders, and a previous history of antioxidant agent use. In addition, patients receiving electroconvulsive therapy were excluded.

Both groups were matched in terms of age, sex, smoking status, and other sociodemographic data. Biochemical tests and inflammatory markers were investigated in all participants, and those with out-of-range levels were not included in the study.

The Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used to evaluate the severity of obsession and compulsion symptoms in patients. The Y-BOCS is a 10-item scale rated between $0-4$, which is administered by a clinician [23].

Thiol/Disulfide Homeostasis

A colorimetric detection method was used to measure the total thiol/native thiol levels following the manufacturer's protocols (Rel Assay Diagnostic, Gaziantep, Turkey).

Detection of total thiol levels

Briefly, 10 µl of serum sample or standard and 10 µl of reagent 1 were mixed in a test tube. Following an incubation period for 100 seconds at room temperature, 110 µl of reagent 2 was added and incubated for 200 seconds at room temperature. The initial absorbance was detected at a wavelength of 415 nm. Then, 10 µl of reagent 3 was added to the mix and incubated for 300 seconds at room temperature. The final absorbance was detected at 415 nm. Total thiol levels were calculated based on the standard curve.

Detection of native thiol levels

Ten µL of serum sample or standard and 100 µl of reagent 1 were mixed in a test tube and incubated for 300 seconds at room temperature. Following the incubation period, the first absorbance was detected at a wavelength of 415 nm. Then, 10 µl of reagent 2 was added to the mix and incubated for another 300 seconds at room temperature. Following the incubation, the final absorbance was determined at 415 nm. Native thiol levels were calculated based on the standard curve. Disulfide levels were calculated by subtracting the native thiol values from the total thiol values and dividing them by two. Disulfide/total thiol, disulfide/native thiol and native thiol/total thiol ratios were calculated and the results were given as percentages [27].

Detection of oxidative DNA damage

In order to detect the oxidative DNA damage, DNA was isolated from leukocytes and 8-OHdG and deoxyguano-sine (dG) levels were measured. Oxidative DNA damage was defined as 8-OHdG/10^6dG. Initially, DNA was isolated from whole blood samples taken from patients and healthy subjects by using commercial DNA isolation kits (Nucleo Spin Blood DNA, RNA and Protein Preparation, Macherey-Nagel, Germany). Isolated DNA samples were hydrolyzed with formic acid, as previously described by Kaur and Halliwell [28]. The concentrations of 8-OHdG and dG of the hydrolyzed DNA samples were determined using the previously described high pressure liquid chromatography (HPLC) method with electrochemical detector (ECD) and variable wavelength detector [29]. Prior to analysis by HPLC, hydrolyzed DNA samples were dissolved in HPLC eluent in a final volume of 1 ml. A total of 20 µl of final lysate was analyzed by HPLC-ECD. A reverse phase-C18 analytical column (250 mm 4.6 mm 4.0 µm; Phenomenex, Torrance, CA, USA) was used. The mobile phase contained 0.05 M potassium phosphate buffer, pH 5.5 and acetonitrile (97:3, v/v) and the flow rate was 1 ml/min. The dG concentration was monitored based on absorption at 245 nm, and the 8-OHdG level was determined based on the ECD reading (600 mV). The dG and 8-OHdG levels were measured using dG and 8-OHdG standards (Sigma Aldrich, St. Louis, MO, USA); The 8-OHdG level was described as 8-OHdG/10^6dG.

Statistical Analysis

The results were analyzed using IBM SPSS 20 package program. Shapiro-Wilks test was used to confirm normal distribution. Independent sample-*t* test and χ^2 tests were

Table 1. Sociodemographic data of the participants

Variable	OCD group (n = 35)	Healthy control group (n = 33)	95 % CI		*p* value
			Lower	Upper	
Sex					0.808
Male	16 (48.5)	17 (51.5)			
Female	19 (54.3)	16 (45.7)			
Age (yr)	27.6 ± 5.03	27.7 ± 5.21	−2.49	2.47	0.995
Education status					0.875
Primary school	4 (50)	4 (50)			
High school	14 (48.3)	15 (51.7)			
University	17 (54.8)	14 (45.2)			
Marital status					0.246
Single	10 (43.5)	13 (56.5)			
Married	25 (55.6)	20 (44.4)			
BMI (kg/m^2)	23.7 ± 1.97	23.8 ± 2.27	−1.16	0.88	0.788

Values are presented as number (%) or mean ± standard deviation.
OCD, obsessive compulsive disorder; CI, confidence interval; BMI, body mass index.

used to compare the differences in both groups. Results were presented as mean ± standard deviation (SD). The rate of significance was determined as $p < 0.05$.

RESULTS

Thirty-five patients with OCD (mean age 27.6 ± 5.03 years) and thirty-three healthy subjects (mean age 27.7 ± 5.21 years) matching in terms of age, sex, and marital status participated in the study. None of the participants were smokers. The mean duration of disease in the patient group was 10.3 ± 8.71 years. According to the Y-BOCS scoring, three patients had mild, sixteen patients had

moderate, twelve had severe, two had very severe OCD symptoms. Two patients were scored subclinical. The sociodemographic characteristics of the participants are summarized in Table 1.

The total and native thiol levels were lower in patients with OCD than those in the control group (Fig. 1). On the contrary, disulfide levels were significantly higher in patients with OCD. The disulfide/total thiol and disulfide/native thiol levels were significantly higher in OCD patients. In addition, 8-OHdG/10^6dG levels, a marker of oxidative DNA damage, were significantly higher in OCD group than the control group (Fig. 2). All values are presented in Table 2.
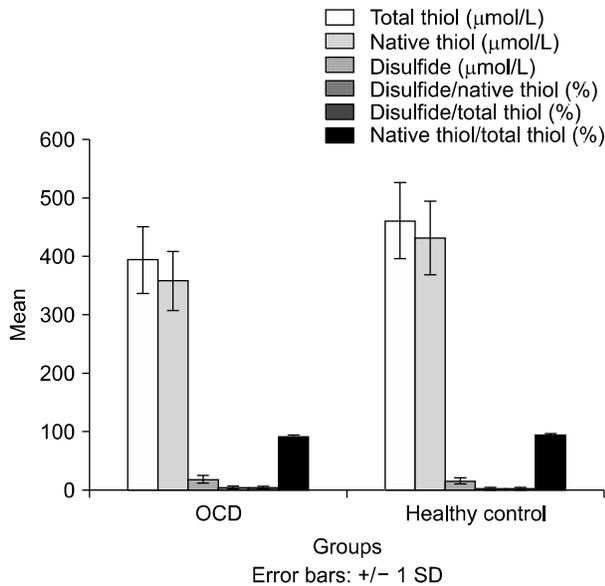
DISCUSSION

Our study is the first study measuring the thiol disulfide balance in patients with OCD and healthy controls and

Fig. 1. Comparison of total thiol, native thiol, disulfide ratios of both groups.
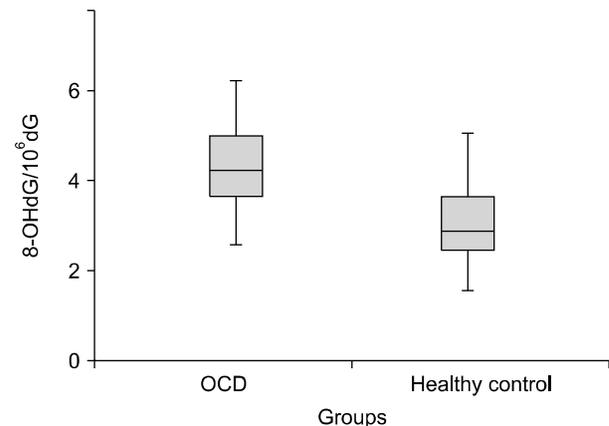SD, standard deviation; OCD, obsessive compulsive disorder.

Fig. 2. 8-OHdG/10^6dG ratios of study and control group.
OCD, obsessive compulsive disorder.

Table 2. Total thiol, native thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol and 8-OHdG/10^6dG ratios of the study and control groups

Variable	OCD group (n = 35)	Healthy control group (n = 33)	95 % CI		p value
			Lower	Upper	
Total thiol (μmol/L)	396.1 ± 58.8	464.6 ± 65.2	−98.2	−38.1	0.001
Native thiol (μmol/L)	358.9 ± 51.1	434.1 ± 60.4	−72.1	−16.1	0.003
Disulfide (μmol/L)	17.9 ± 6.87	14.1 ± 5.09	0.72	6.76	0.016
Disulfide/native thiol (%)	5.01 ± 1.84	3.28 ± 1.13	0.94	2.48	0.001
Disulfide/total thiol (%)	4.49 ± 1.52	3.06 ± 1.01	0.78	2.07	0.001
Native thiol/total thiol (%)	90.7 ± 3.44	93.8 ± 2.01	−4.56	−1.74	0.008
8-OHdG/10^6dG	4.26 ± 1.11	2.74 ± 0.98	0.66	1.68	0.001

Values are presented as mean ± standard deviation.
OCD, obsessive compulsive disorder; CI, confidence interval.

evaluating them all together. We showed that total and native thiol levels were significantly low but disulfide levels were significantly high in patients with OCD compared to the control group. Another major outcome was that the disulfide/total thiol and disulfide/native thiol levels were significantly high in OCD patients but native thiol/total thiol levels were significantly high in control group. Apparently, thiol disulfide balance had shifted in favor of disulfide in patients with OCD.

The first target of reactive oxygen species (ROS) is the -SH group of the cysteine that is in structure of proteins. As these structures are attacked by ROS, -SH is oxidized to disulfide, and the function of the protein is lost. Thiol-containing compounds such as glutathione are important parts of the organism's antioxidant defense system. In addition, they are important for apoptosis and stabilization of proteins. Determining the shift of thiol/disulfide balance can be useful for having knowledge about oxidative state of the organism. Ates *et al.* [30] have shown that thiol/disulfide homeostasis has been impaired in diabetic patients, and Altıparmak *et al.* [31] have demonstrated that this balance has been impaired in favor of disulfide in patients with coronary artery disease. In the oxidative balance study of Erzin *et al.* [27] which has been conducted in patients with bipolar disorder, it has been reported that levels of native thiol have decreased in manic attack group compared to the remission group. In another study of Erzin *et al.* [32], they have emphasized that thiol/disulfide balance has been impaired in favor of disulfide in patients with unipolar and bipolar depression. Unal *et al.* [33] have investigated the thiol/disulfide homeostasis in patients with schizophrenia and they have shown that native thiol and total thiol levels were significantly lower, but disulfide and disulfide/native thiol levels were significantly higher in schizophrenic patients. A number of studies have suggested that this balance has shifted towards disulfide in neurological disorders such as epilepsy and migraine [34,35]. Another study has suggested that this balance has changed in patients with anxiety disorder, another psychiatric disorder, and disulfide levels have increased compared to the control subjects [36].

In our study, levels of 8-OHdG were significantly high in the OCD group. Unlike previous studies, we did not detect 8-OHdG levels in serum, plasma or urine, but detected 8-OHdG levels in DNA in order to assess the DNA damage in patients with OCD, and to do this, we used a more sensitive method, that is HPLC method. Unless the base modifications caused by the attack of ROS are not corrected by DNA repair genes, they cause mutations in DNA, thus the function of proteins encoded by these genes are lost, which may lead to serious complications. A body of evidence has shown that the structure of lipids and proteins in cell membrane and DNA can be irreversibly damaged. Both nucleus and mitochondrial DNA are major indicators of 8-OHdG damage, which is constantly caused by oxygen radicals [20]. Post-mortem examinations have demonstrated that increased levels of 8-OHdG in cranial tissues samples and bodily fluids are associated with many degenerative diseases and carcinogenesis. Brain tissue, a major consumer of oxygen, is highly susceptible to oxidative damage [37]. In post-mortem studies, 8-OHdG has been determined as an indicator of oxidative DNA damage in psychiatric diseases such as schizophrenia, bipolar disorder, and major depression [37]. Post-mortem studies of schizophrenics have shown that serum levels of 8-OHdG have increased by 10-fold in the hippocampus [38]. High levels of serum 8-OHdG have also been reported in patients with major depression [39]. In addition, it has been reported that patients with recurrent depressive episodes have more oxidative DNA damage than patients with a single episode [40].

In our study, there was a negative correlation between oxidative DNA damage, total and native thiol, and levels of 8-OHdG/10^6dG had increased but levels of total and native thiol had decreased. The decline in levels of antioxidative parameters indicates that this may damage the DNA structure. A previous study has stated that there was no significant relationship between oxidative stress parameters, levels of oxidative stress and DNA damage in patients with schizophrenia [41]. In another study investigating the relationship between oxidative stress and DNA damage in patients with depression, it has been stated that oxidative DNA damage has increased in patients with depression [42]. A recent study has investigated the relationship between the levels of DNA damage and oxidative stress in child and adolescent victims of sexual abuse with or without post-traumatic stress order and no difference between the two groups has been reported [43]. Significantly high levels of oxidative stress and oxidative DNA damage in patients with OCD have led us to think that stress related DNA damage can accelerate aging. Pharmacological treatments, cognitive therapies,

treatment of sleep problems, regular exercise or administration of natural antioxidants in the early stages of treatment of the OCD patients may help regulate the thiol/disulfide balance and prevent oxidative DNA damage.

Limitations of the study: Since our study was a cross-sectional study, it was difficult generalize the results. Although we tried to homogenize the groups, the number of patients in each group was low, and we were not able to divide the groups in sub-groups in terms of medication as there was a large spectrum of drugs used by the patients. Furthermore, due to the low number of patients in the OCD group, the patients could not be classified according to the severity of the disease. In addition, we were unable to eliminate factors that may affect levels of oxidative stress such as family medical histories, diet and sleep patterns, exercise status, and working conditions of the participants.

To conclude, we showed that the thiol/disulfide balance has shifted in favor of disulfide in patients with OCD compared to healthy controls and that 8-OHdG levels, indicators of DNA damage, were higher in OCD patients than the control subjects. Inflammation has been reported in cortico-striatal circuitry in patients with OCD [44], and this may be associated with increased levels of oxidative stress. Oxidative stress is particularly and closely related to inflammatory pathways. Pro-inflammatory cytokines are produced in response to oxidative stress, and oxidative stress enhances the inflammatory response [45]. Regulation of oxidative stress balance in OCD patients would be helpful in treatment, and in reducing morbidity.

Based on these results, OCD patients who are treated regularly or irregularly and those who do not receive any treatment should be monitored closely and measurements should be performed. In addition, patients who have been diagnosed a long time ago and recently should be compared. The patients should be examined in terms of how disease duration, treatment status and levels of oxidative stress affect them.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Design the study and Writing ─ protocol: Faruk Kurhan. Data acquisition: Faruk Kurhan, Yavuz Selim Atan. Statistical analysis: Hamit Hakan Alp, Faruk Kurhan. Design of the protocol: Hamit Hakan Alp. Writing ─ original draft: Mesut Işık. All authors interpreted the results and helped revise the manuscript.

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